REMARKS

Claims 1-66 are pending. Claims 23-58, and 64-66 are withdrawn from consideration. Claims 1-22 and 59-63 are rejected. Claims 1 and 6 have been amended, as supported by the disclosure in the paragraph bridging pages 9 and 10. Claims 1-66 remain in the case.

Claims 1-10, 13-22, and 59-63 stand rejected under Section 103(a) based on Carr *et al.*, and claims 1-22 and 59-63 stand rejected under Section 103(a) based on Carr *et al.* in view of Girot *et al.* The examiner states that:

> the lowest porosity explicitly disclosed is 31%, which occurs
> at a sintering temperature of 900 degrees. It is considered that
> it would have been obvious to one of ordinary skill in the art
> to have made the porosity < 30%. Carr et al. ('373) discloses
> that "the surface area and pore volume decrease with
> increasing firing temperature" (col. 13, lines 37-39) and also
> that the sintering temperature can range for 100-1500 degrees
> (col. 8, lines 20-29). This would suggest to one of ordinary
> skill in the art to decrease the porosity below 30%.

In rebuttal of the examiner's position, applicants submit with this response the declaration of Dr. Egisto Boschetti, one of the inventors of the present application. Dr. Boschetti details why the disclosure of Carr *et al.* would not have led one of ordinary skill to decrease porosity, or pore volume, below 30%. More particularly, he notes that the examiner's rationale presumes that the prior art illustrated by Carr would have prompted the skilled artisan to pursue the goal of reducing pore volume for a chromatography medium of the sort prescribed in the claims of the application. Speaking as one of skill in the field of chromatography, however, he attests that the statements that the examiner highlights from Carr neither suggest, from context, any advantage to this goal nor provide guidance on how it is to be achieved.

It is Dr. Boschetti's opinion, speaking as an expert in the field of chromatography, that Carr does not lead a skilled artisan to produce mineral oxide beads with a pore volume of less than 30%. To the contrary, he attests that Carr suggests to him that pore volume and pore size both should be maximized, and he identifies various statements in Carr which

suggest to him that pore volume should be maximized, and not controlled to values of less that 30%. The goal in Carr of maximizing pore volume is further bolstered by the intended use for Carr's media, which likewise suggest to Dr. Boschetti and others in the field that larger pore volumes are desirable. Namely, Carr discloses a media for separation of proteins, particularly antibodies, and Carr's methodology entails entry into the pores of the medium by the proteins to be separated. Increased pore diameter and pore volume together allow more of the proteins that are to be separated to diffuse freely into the internal void volume, thereby reaching all available surface area, which also should be maximized. Based on the end use for beads, Carr's desire to maximize pore volume is logical.

Dr. Boschetti further attests that Carr fails not only to suggest mineral oxide beads with a pore volume less than 30% but also to disclose any advantage associated with such beads. Hence, a reader of Carr would not be motivated to produce such beads. In contrast, he details three advantages of beads according to the present invention. First, low pore volume material firmly anchors an interactive polymer network on the beads - to provide a polymer network that is firmly rooted in the pores. While the emphasis in Carr is on large pore diameters and pore volume, to allow free access to the interior of proteins to be separated, the pore volume according to the invention is just large enough to allow polymers to be rooted in the pores. Thus, the prescribed pore volume is related directly to the disclosed purpose of firmly anchoring an interactive polymer network that is crosslinked in the pores. The interaction of the desired molecules occurs on the external surface area of the beads due to the rooted polymers. The role of the pores is to provide just enough space inside the beads to anchor the polymer. The crosslinked polymer will be exposed only at the external bead surface where the interaction with large macromolecules occurs. "Rooting" of the polymer is needed because the external layer of polymer responsible for the interaction with macromolecules must be stable. According to the invention claimed in the application, it is stabilized in place as a tree that is rooted in its substrate.

Second, a small pore volume minimizes the diffusion of small molecules into the pores. A large pore volume as in Carr allows small molecules to diffuse inside the beads, instead of leaving the column with the source liquid. When small molecules diffuse inside

the pores, they can be eliminated only by using long and repeated washings. The diffusion of molecules within the secondary network created by the polymer is not completely prevented, but is significantly reduced in particular with mineral oxides possessing pore volumes less than 30%, and it is reduced even more when the pore volumes are less than 25% or 15%, two preferred embodiments of my invention. In particular, when pore volume is less than 15%, diffusion of small molecules is so restricted that it is almost non-existent. A small pore volume thus results in a second advantage that Carr does not suggest.

Finally, the smaller the pore volume, the larger the particle density. Density is an advantage particularly in the context of fluidized bed technologies, one of the intended uses of the present beads. This third advantage also is not suggested by Carr.

Dr. Boschetti further attests that Carr fails to teach an interactive, crosslinked polymer network that fills the pores and is coated on the external surface of the mineral oxide matrix, such that subsequent interaction with macromolecules occurs on the external surface area of the support, as is the case with the invention claimed in the application. He states his understanding that the polymer in Carr coats but does not fill the pores. In support of this interpretation, he highlights a statement, at the bottom of column 5 of the Carr reference, that the ZrO_2 spherules "bioactive materials can be strongly sorbed onto the exterior and *interior surfaces of* both the uncoated and *the polymer-coated ZrO_2 spherules*, while retaining a large percentage of their initial bioactivity. Useful biomaterials include proteins such as enzymes and antibodies" (emphasis added). The fact that there are "interior surfaces of the polymer-coated ZrO_2 spherules" clearly shows that the beads are different than the beads as presently claimed in which an interactive crosslinked polymer network fills the pores and is coated on the external surface of the mineral oxide matrix, so that subsequent interaction with macromolecules occurs on the external surface area of the support.

The examiner adds Girot to Carr in rejecting some of the claims. Dr. Boschetti is a co-inventor of Girot and, hence, is in a particularly good position to shed light on its

disclosure. He attests that the purpose of the subject matter described in this patent is to have a hydrogel fill the pores of mineral oxides entirely, while allowing even macromolecules still to diffuse inside. Therefore, the pore volume is made as large as possible, to maximize the binding capacity of the final material. This approach contrasts sharply with that described in the application. The latter strives to foreclose access to the pore volume by the molecules in the source solution, and it uses a small pore volume in order that a crosslinked polymer can be stably rooted in the matrix and that interactions should occur on the surface of the bead.

Based on the attestations of an expert in the field of chromatography, and prior responses of record, reconsideration and withdrawal of the rejections under Section 103(a) are requested. In view of the foregoing remarks, it is believed that all claims are in condition for allowance. Reconsideration of all rejections and a notice of allowance are respectfully requested. Should there be any questions regarding this application, the examiner is invited to contact the undersigned attorney at the phone number listed below.

Respectfully submitted,

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VERSION WITH MARKINGS TO SHOW CHANGES MADE – CLAIMS

1.   (Twice Amended) Dense mineral oxide solid supports comprising:

(a)   a mineral oxide matrix having an external surface and pores, wherein the pores have a pore volume which is less than 30% of the total volume of the mineral oxide matrix, and

(b)   an interactive polymer network which [is crosslinked inside] <u>fills</u> the pores and <u>is coated</u> on the surface of the mineral oxide matrix<u>, so that subsequent interaction with macromolecules occurs on the external surface area of the support</u>.

6.   (Twice Amended) Dense mineral oxide solid supports comprising:

(a)   a mineral oxide matrix having an external surface and pores, wherein the pores have a pore volume which is less than 30% of the total volume of the mineral oxide matrix, and

(b)   an interactive polymer network which [is crosslinked inside] <u>fills</u> the pores and <u>is coated</u> on the surface of the mineral oxide matrix<u>, so that subsequent interaction with macromolecules occurs on the external surface area of the support,</u>

wherein said dense mineral oxide solid supports have a density of 2.1 to 11, and a particle size of 10 μm to 100 μm.